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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/07/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/849,626	BANGUR ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-13 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 19-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IX, claim 14, and SEQ ID NO: 1797 in Paper No. 9 is acknowledged. With regard to the election of the SEQ ID NO, as noted in the restriction requirement, this is NOT a species election. Each SEQ ID NO is a separate invention and properly restricted because they differ in structure and function. Therefore, the election of the specific SEQ ID NO is election of an invention, not a species, and species practice does not apply. Claims 1-13 and 15-18 are withdrawn from further consideration.

Claim Rejections - 35 USC § 112 - Description

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 14 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in

possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification, specifically, any oligonucleotide which hybridizes under moderately stringent conditions to SEQ ID NO: 1797. The specification on page 87 does discuss moderately stringent conditions but permits a temperature range between 50 and 60 degrees, and indicates that the specified conditions are simply for illustration. Even relying upon the conditions in the specification, nearly every oligonucleotide which comprises perfectly matching 22 mer will meet this stringency language. So while there are only 4578 perfectly matching 22 mers, there would be 4.8×10^9 different 32 mers which would contain 22 described nucleotides and 10 unknown and unpossessed nucleotides. This calculation does not even include the much larger number of mutations possible within the probe regions. This large genus is represented in the specification by only the particularly named SEQ ID No. Thus, applicant has express possession of only one sequence, SEQ ID NO: 1787, in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed, not even the presence of certain domains. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations is provided. Further, these claims encompass alternately spliced versions of the proteins,

allelic variants including insertions and mutations, inactive precursor proteins which have a removable amino terminal end, and only one specific nucleic acid sequence has been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, where the definition of the possible probes lack any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the full length sequence, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to anything which hybridizes to SEQ ID NO: 1797, for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a deletion, without any definition of the particular changes claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 - Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 14 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. .

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of diagnosing lung cancer by detection of an expressed polynucleotide that hybridizes to a probe which hybridizes to SEQ ID NO: 1797. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of detection of lung cancer in patients by analyzing whether a probe which can hybridize to SEQ ID NO: 1797 hybridizes to the sample above a cut off value. The method broadly encompasses the use of the method in any of the many different types of lung cancer and in any type of mammalian

patient. For example, just among the non-small cell lung cancers, there are squamous cell carcinomas (SQC), large cell cancers (LGC), adenocarcinomas (ADC) and bronchioloalveolar carcinomas. Further, the cells undergoing the test may be subject to any of a variety of different conditions depending upon the particular patient studied, with insulin dependent patients, for example receiving daily doses of a compound which significantly alters cellular metabolism while cancer patients may be receiving chemotherapeutic treatments, pain medicine for surgery, corticosteroids to reduce trauma associated with surgery which themselves significantly impact cellular metabolism or any of a number of other complicating factors which impact the expression of cellular markers such as SEQ ID NO: 1797.

Quantity of Experimenation

The quantity of experimentation in this area is large since there is significant variability in the expression of SEQ ID NO: 1797 depending upon the cell type, cell environment as discussed above regarding chemotherapeutic or other treatments which is an inventive, unpredictable and difficult undertaking in itself, and efficacy of SEQ ID NO: 1797 as a prognostic marker for cancer requires more than a showing that it is overexpressed in four cell lines, which may not themselves be representative of actual biopsied patients. Il would need to be demonstrated in a variety of different cell type models. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art teaches several factors are significant in analyzing whether a marker will be diagnostic for a particular disease. For example, Welsh et al (PNAS (2001) 98(3):1176-1181 teach that "Good tumor markers fulfill several criteria, including low expression in normal tissue and high expression in neoplastic tissue. Markers should also exhibit a clear cutoff in expression levels between normal and neoplastic tissues to unambiguously resolve the two diagnostic conditions. (page 1179, column 2)". The current specification fails to resolve these issues regarding SEQ ID NO : 1797, since it presents no data to show the relative expression between normal and neoplastic tissue and no specific cutoff is provided in the specification.

This absence of a cutoff is one of the most unpredictable elements of this invention. In the absence of any guidance from the specification or the prior art, it is entirely unpredictable what cutoff should be selected to distinguish between normal and neoplastic lung cancer tissue. Further, no evidence is present that such a cutoff exists for SEQ ID NO: 1797.

Separately, Welsh notes that "As illustrated above, some of the tumor samples exhibited strong signals from genes characteristic of stroma and/or infiltrating immune cells. This observation suggested that they contained a low fraction of epithelial cells, which was confirmed by histology. Because we sought genes whose expression was diagnostic of malignant epithelium, 14 of the 27 tumors were excluded from this analysis based on their "non-epithelial" expression patterns. (page 1179, column 2)." In this excerpt, Welsh exemplifies the unpredictability of this art. More than half of the tumors studied, (unlike the specification, here actual tumors were examined) were unsuitable for analysis due to their expression patterns. This further demonstrates the unpredictability of diagnosis in this area when the specific types of lung cancer, such as

squamous cell carcinomas (SQC), large cell cancers (LGC), adenocarcinomas (ADC) and bronchioloalveolar carcinomas are not separately analyzed, when the cell source is not tumor tissue and when the analysis is not shown to be statistically significant. Thus, the ordinary practitioner would expect significant unpredictability in applying SEQ ID NO: 1797 to prognosis or diagnosis of any of the many types of lung cancer.

Working Examples

The specification has a single working example where SEQ ID NO: 1797 is shown to be overexpressed in 4 out of 7 cell lines (assuming that the statement in the election is correct, since page 172 indicates that L978P is actually associated with SEQ ID NO: 1339), but the working example was not demonstrated to be linked to actual patient samples or to any statistically significant number of cancers.

Guidance in the Specification.

The specification, while suggesting the that SEQ ID NO: 1797 is lung cancer associated, did not provide significant guidance on the association. The specification failed to discuss any correlation at a statistically significant level between lung cancer and SEQ ID NO: 1797. The specification provided no specific cutoff value for the association of SEQ ID NO: 1797 and lung cancer, as required by claim 14. The specification did not indicate whether SEQ ID NO: 1797 was, in fact, lung cancer specific or was general to all cancers, to all growing cells or to some other subset of cells in which lung cancer might fall, even failing to disclose whether the expression was increased relative to normal lung.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching of unpredictability by the art is opposed to patentability (see Welsh above). The specification provides one with no written description or guidance that leads one to a reliable method using SEQ ID NO 1797 as a diagnostic agent for lung cancer. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Further the specification does not provide guidance to overcome art recognized problems in the use of molecular markers which are undefined as detection agents. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the test and the negative teachings in the prior art balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1637

November 5, 2002